Abstract: P1575

Title: TOPLINE RESULTS OF THE AURORA TRIAL: A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF BITOPERTIN IN ERYTHROPOIETIC PROTOPORPHYRIA

Abstract Type: Poster Presentation

Topic: Iron metabolism, deficiency and overload

Background:

Erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLP) are caused by pathogenic variants in the ferrochelatase (*FECH*) or 5-aminolevulinate synthase 2 (*ALAS2*) genes, respectively, resulting in accumulation of photoreactive protoporphyrin IX (PPIX). In the protoporphyrias, elevated levels of PPIX cause debilitating phototoxic skin reactions following exposure to sunlight and may lead to potentially life-threatening protoporphyric hepatopathy in some patients. Reduction of PPIX is associated with amelioration of disease in the settings of hematopoietic stem cell transplant, pregnancy, and extracorporeal photoinactivation.1-3

Glycine transporter 1 (GlyT1) supplies extracellular glycine for the initial step of heme biosynthesis in erythroid cells.4 Bitopertin is an investigational small molecule inhibitor of GlyT1. It is hypothesized that GlyT1 inhibition leads to a decrease in heme pathway intermediates, including PPIX, and can improve light tolerance.5 In murine models of EPP and XLP, treatment with bitopertin lowered blood PPIX levels by >40% compared to controls.6 Bitopertin treatment in mice with EPP also lowered liver PPIX levels and reduced histopathological evidence of liver cholestasis and fibrosis compared to controls.7 Initial data from an open-label study of bitopertin in 22 adults with EPP or XLP (BEACON; ACTRN12622000799752) showed that treatment with bitopertin resulted in mean reductions in PPIX >40 % ($p<0.001$), which translated to meaningful improvements in sunlight tolerance and improvements in patientreported quality of life.8

These data, combined with a favorable safety profile observed in prior clinical studies of bitopertin with cumulative enrollment of >4000 participants, provided rationale for AURORA.

Aims:

Evaluate the safety, tolerability, and efficacy of bitopertin in adults with EPP. Efficacy assessments include changes in levels of whole-blood metal-free PPIX, as well as measures of phototoxicity, sunlight tolerance, and pain.

Methods:

AURORA is a Phase 2, randomized, double-blind, placebo-controlled trial (NCT05308472) that randomized 75 participants (1:1:1) to receive oral, once-daily administration of 20 mg, 60 mg bitopertin, or placebo for 17 weeks. Participants ≥18 years of age with a confirmed diagnosis of EPP by PPIX analysis and/or genetic testing were enrolled. Exclusion criteria included alanine aminotransferase/aspartate aminotransferase values ≥2x the upper limit of normal, hemoglobin <10 g/dL, or concurrent treatment with afamelanotide or dersimelagon. Randomization was stratified by baseline light tolerance (time to prodrome < or ≥30 minutes), as assessed during a 2week screening period.

The primary endpoint is percent change from baseline in whole blood metal-free PPIX in participants randomized to bitopertin compared to placebo. The key secondary endpoint is the total hours of sunlight exposure to skin on days with no pain from 10:00 to 18:00 hours. Upon completion of the double-blind treatment period, participants may continue in an open-label extension study.

Results:

Unblinded topline safety and efficacy data, including changes from baseline in wholeblood metal-free PPIX and

measures of light tolerance, will be presented.

Summary/Conclusion: Bitopertin has been shown to significantly reduce PPIX levels in prior clinical and nonclinical studies of EPP. The AURORA trial evaluates whether reductions in PPIX with bitopertin can improve measures of light tolerance in adults with EPP. Topline safety and efficacy data will be presented.

Keywords: Iron metabolism, Heme, Clinical trial